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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/982,120	10/17/2001	Sanford M. Simon	600-1-280N	9363

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/982,120	SIMON ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-53* is/are pending in the application.

4a) Of the above claim(s) *33-51 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21-32 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/25/05 has been entered. Applicant's amendment and response and the declaration under 37 CFR 1.132 also received on 3/25/05 have been entered. Claim 20 is canceled. Claims 1-19 and 21-53 are pending in the instant application. This application contains claims 33-51 and 53 drawn to an invention non-elected with traverse in applicant's submission dated 10/10/03. Claims 1-19, 21-32, and 52 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC § 112

The rejection of claims 1-19, and 21-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. Applicant's amendments and arguments have

been fully considered but have not been found persuasive in overcoming the instant grounds of rejection as discussed in detail below.

The applicant argues that the amendments to independent claims 1 and 17 have overcome the grounds of rejection set forth in the previous office. However, the office does not agree that the claim amendments have overcome the indefiniteness of the claims. As amended, the claims now recite a genetically-modified non-human mammal or immune cell produced from said mammal which contains a genetic construct having a single vector comprising a fusion polynucleotide comprising an immunoglobulin component and at least one detectable protein wherein said non-human mammal or cell is capable of expressing at least one chimeric immunoglobulin gene. The claims as amended are still confusing for the following three reasons. 1) it is unclear what is meant by " a genetic construct having a single vector". A vector is a type of genetic construct, as such the metes and bounds of the claim are unclear because either the claim is now confusing because it is unclear what elements, other than the vector, it might contain. 2) The claims now recites that a fusion polynucleotide comprising an immunoglobulin component selected from a group consisting of the kappa Ig light chain, the lambda Ig light chain, and an Ig heavy chain. The light chain, and heavy chain refer to protein, not nucleic acid, and as such the claim is confusing as it is unclear how the polynucleotide comprising the identified proteins. The same problem applies to the detectable protein, since it is unclear whether the applicant intends the claims to recite that the fusion polynucleotide is somehow complexed with the detectable protein or whether the fusion polynucleotide comprises a gene encoding a detectable protein. It is suggest that the claim be amended to recite light chain and heavy chain **genes**, and a **gene encoding** a detectable protein. 3) The claims as amended now

lack antecedent basis for "at least one chimeric immunoglobulin gene" and " at least one detectable protein or peptide" because the claim now refers to fusion polynucleotides, not chimeric immunoglobulin genes, and further because the fusion polynucleotide comprises a detectable protein, not a detectable peptide. The difference in language further renders the claims indefinite because it is unclear whether " the fusion polynucleotide " is the same as the "chimeric immunoglobulin gene". Claims 2-16, 18-19, and 21-32 depend on claims 1 and 17 and thus are included in this rejection.

Further in regards to claim 17, the claim is confusing in the recitation, "wherein said at least on detectable protein is present at the C-terminus of the gene product of said fusion polynucleotide with a flexible linker therebetween". The fusion polynucleotide comprises an immunoglobulin component and a detectable protein, so the gene product of this fusion polynucleotide already comprises a detectable protein, therefore it is confusing where the flexible linker is supposed to be located. It is suggested that the claim be amended to recite that the flexible linker is located between the immunoglobulin component and the detectable protein.

Furthermore, dependant claims 7-9 and 23-25 now lack antecedent basis for "an immunoglobulin molecule". Amended claims 1 and 17 no longer refer to an immunoglobulin molecule.

In addition, claims 18 fails to further limit claim 17. Claim 17 already recites that the detectable protein is present at the C-terminus of the gene product of said fusion polynucleotide.

Claim Rejections - 35 USC § 102

The rejection of claims 17-19 and 22-25 under 35 U.S.C. 102(b) as being anticipated by Fell et al. is withdrawn in view of the limitation in claims 17-19 and 22-25 that gene product of the fusion polynucleotide comprises a flexible linker peptide.

Claim Rejections - 35 USC § 103

The rejection of claims 21 and 27-30 under 35 U.S.C. 103(a) as being unpatentable over Fell et al. in view of Casey et al. is **maintained over pending claims 17-19, 21-25 and 27-30**. Applicant's amendment and arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant first argues each reference separately and concludes that neither Fell et al. nor Casey et al. teach the making of cells in vivo as recited in claims as amended, and further that Fell et al. teaches using two vectors rather than the single vector now recited in the claims. As noted in the previous office action, claims 17-19, 21-25, and 27-30 are product by process claims. The applicant argues that Fell et al. teaches an *in vitro* method for producing genetically modified antibody producing cells and does not teach the *in vivo* method disclosed by applicants. The applicant further argues that Fell et al. uses a two vector system to modify the genome whereas in the instant invention uses only a single vector. As discussed in the previous office action, the applicant is reminded that "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the

product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). Thus, Fell et al. is not required to teach making the cells using the exact method used by applicants as long as the cells made are the same. In the instant case, Fell et al. teaches genetically modified antibody producing cells in which a component of an immunoglobulin gene has been replaced with a portion of the human variable or constant gene linked to an enzyme or substrate such as betagalactosidase, alkaline phosphatase, or horseradish peroxidase (Fell et al., column 11, lines 24-66, and column 12, lines 1-12). Fell et al. discloses that the antibodies produced by these cells are detectable and can be used as labeled antibodies in diagnostic assays without further modification (Fell et al., column 11). Fell et al. further teaches that the replacement gene can be inserted into either or both of the light chain or heavy chain immunoglobulin genes (Fell et al., column 10). In addition, Fell et al. teaches that the replacement gene can be linked to the C-terminus of the chimeric immunoglobulin (Fell et al., Figures 1B + 1C). Fell also teaches a specific embodiment where the replacement gene encodes all or a portion of IgG1, such that the linked enzyme is present in exon G1 (Fell et al., column 14, lines 55-67). Thus, Fell et al. teaches cells with the same structural and functional limitations as the cells recited in the claims with the exception of the flexible linker. Casey et al. has been cited for providing the teachings and motivation to use a flexible linker between the immunoglobulin gene and the detectable marker. Furthermore, contrary to applicant's assertions, Fell et al. does in fact teach using a single targeting vector for homologous recombination, see Figures 1A-1C and columns 8-9). Figure 1 in particular shows how a single targeting vector can homologously recombine with the genomic

DNA to insert the replacement gene into either the constant region or variable region of either the immunoglobulin light chain or heavy chain genes. Thus, applicant's arguments regarding the differences between the Fell method for making the modified immunoglobulin producing cell and the applicant's methods are not persuasive for the instant product by process claims.

The applicant further argues that Casey et al. does not teach the detectable proteins claimed in claim 27, that the bacterial system used by Casey does not allow for proper glycosylation to maximize function and specificity of the antibodies produced, and that Casey et al. teaches away form the instant invention by using a single chain antibody variable fragment rather than a whole antibody. In response, Casey et al. was cited for teaching the construction of detectable antibody by transfecting cells with a vector encoding a single chain antibody operably linked to a flexible glycine linker and GFP (Casey et al., page 446, Figure 1, construct iv). Please note that GFP is an autofluorescent protein and as such meets the claims limitations of claims 27-29. The fact that Casey et al. used bacterial cells to produce the antibody is not relevant, since the antibodies produced by Casey et al. were fully functional in recognizing and binding specific antigen, the claims do not require any particular level of activity or glycosylation, and Fell et al. provides the primary teaching for producing antibodies in mammalian cells, which would necessarily provide the correct glycosylation. Further, Casey et al. was cited for providing motivation for substituting the flexible linker-GFP marker for the beta-galactosidase marker taught by Fell et al. by teaching that fluorescent labels provide high levels of sensitivity for a wide range of analytical assays (Casey et al., page 445). Thus, the skilled artisan would have been motivated to substitute the nucleic acid sequence encoding the flexible linker-GFP taught by Casey et al. for the nucleic acid sequence encoding the beta-galactosidase detectable marker

in the construct taught by Fell et al. based on the high level of sensitivity in detecting GFP and on the fact that fluorescent antibodies can be directly detected without the need to treat the cells or purified antibodies with additional reagents such as X-gal in the case of beta-galactosidase. Regarding the alleged "teaching away" by Casey et al. because Casey et al. produced single chain antibody, the applicant appears to base this argument on the fact that a complete antibody comprising two complete light chains and two complete heavy chains is larger than a single chain antibody. However, the claims as written simply recite that the detectable protein is linked to an antibody heavy or light chain and that the cells produce antibody. A single light chain is no larger than a single chain variable fragment of an antibody. Further, it is again noted that the claims as written include no limitations regarding the functionality of the produced detectable antibody. In addition, since the detectable ScFv produced by Casey et al. was in fact fully functional, there exists a reasonable expectation that the addition of a detectable marker to a light chain in a regular antibody would not alter the function or specificity of the antibody containing this light chain.

The rejection of claims 1-9, 11-14, and 52 under 35 U.S.C. 103(a) as being unpatentable over Fell et al. in view of Casey et al. and Rajewsky et al. is maintained. Applicant's amendment and arguments, and the declaration under 37 CFR 1.132 by Sanford Simon have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Applicant's arguments directed to the teachings of Fell et al. and Casey et al. have been addressed in detail above. The applicant further argues that Rajewsky et al. does not teach in

vivo methods of generating detectable labeled antibodies. In response, it is reiterated that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Fell et al. in view of Casey et al. were already cited for providing the teachings and motivation to make genetically modified cells capable of expressing detectably labeled antibodies comprising various detectable markers including enzymatically active marker proteins and fluorescent marker proteins. The previous office action stated that Fell et al. in view of Casey et al. differ from the instant claims in that neither teach making a genetically modified mammal to express the chimeric labeled antibodies. Rajewsky et al. was cited for providing motivation for making transgenic mammals to produce chimeric antibodies *in vivo* over the *in vitro* methods of producing antibodies taught by Fell et al. Rajewsky et al. is not required to teach making detectable antibodies since that teaching has already been provided by Fell et al. and Casey et al. Rajewsky et al. teaches methods of making transgenic mammals comprising genetically modified chimeric immunoglobulin and provides specific motivation for producing chimeric antibodies *in vivo* over *in vitro* methods based on the drawbacks to *in vitro* methods of antibody production including the cumbersome work required to generate specific monoclonal antibodies of appropriate biological function and the difficulty in producing large quantities of these antibodies (Rajewsky et al., column 1). Rajewsky et al. teaches that the use of transgenic mice overcomes these obstacles since every cell possesses the inserted replacement gene such that exposure to different antigens will produce chimeric antigen-specific antibodies in quantities substantially larger than the amount capable of being expressed by cells in tissue culture. Therefore, based on the benefits of producing chimeric antibodies using

transgenic mice over recombinant cells in tissue culture, it would have been *prima facie* obvious to the skilled artisan at the time of filing to use the homologous recombination vector taught by Fell et al. to produce transgenic mice according to the methodology taught by Rajewsky et al.

In regards to applicant's arguments regarding the insertion of two different detectable markers, such as a fluorescent marker and an enzymatic marker, it is noted that claims directed to the insertion of two different detectable marker genes have not been included in this rejection.

Further in regards to applicants' argument that Casey et al. establishes potential problems with protein folding, it is noted that despite these potential problems, the labeled antibody produced by Casey et al. was in fact fully functional. Thus, the potential problems with protein folding did not in fact occur when a detectable label was attached to antibody. Thus, Casey et al. does not teach away from linking detectable markers, including GFP, to antibodies.

As noted above, the declaratory evidence presented in the Declaration under 37 CFR 1.132, including the attached supporting references, have been fully considered with deference to the opinions of the inventor. The applicant argues that the declaratory evidence establishes that the skilled artisan would not have had a reasonable expectation of success in producing detectably labeled antibodies *in vivo* according to the instant invention. In support of this argument, the declaration cites several references in which the applicant states that attempts to detectably label proteins has failed to produce functional proteins. In response, it is first noted that none of claims as written include any limitations concerning the functionality of the produced antibodies. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, none of the provided references are directed to the

labeling of antibodies. The majority of the references cited as evidence were in fact published after the effective filing date of the instant application and thus cannot be used to establish the state of the art and reasonable expectation of success at the time of filing. Further, the few references cited which were published prior to the priority date of this application do not support applicant's position regarding the unpredictability of expressing functional proteins fused to GFP or other detectable markers. The Doyle reference, which discusses actin-GFP, actually shows that of 3 fusion proteins produced, only the actin-GFP fusion was less than fully functional. In the Cubitt references, the majority of fusion proteins made with GFP were in fact functional, see Table II. Thus, reading Cubitt and Doyle, the artisan would in fact reasonably expect that a fusion protein made with GFP could be produced in cells and function appropriately. Furthermore, the Casey et al. reference cited in the instant rejection clearly demonstrates that a fusion protein of a single chain antibody and GFP properly folds and is fully functional. Thus, direct evidence exists in the prior art that functional fusions of GFP and antibody could be produced. Therefore, based on the evidence as a whole which was available to the skilled artisan at the time of filing, the office concludes that the skilled artisan would in fact have had a reasonable expectation of success at the time of filing in producing fusion antibodies by following the combined teachings of Fell et al., Casey et al., and Rajewsky et al.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be

reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER